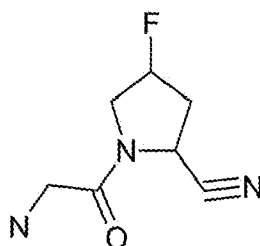


Applicants traverse the Election/Restriction. Applicants respectfully submit that this twenty-two way restriction as imposed by the Examiner is improper based on the following grounds:

1. The Election/Restriction is improper because it divides a Markush claim relative to the variables thereof rather than adhering to the requirement of PCT Rule 13.1 and 13.2.
2. The Examiner's characterization of the "special technical feature" is unduly limiting.
3. The lack of unity of invention imposed on the corresponding PCT Application No. PCT/HU03/00017 does not correlate with the instant restriction requirement.
4. Products, processes of making them and their uses should be rejoined pursuant to MPEP 821.04
5. The restriction requirement imposes undue expense and discourages Applicants from maintaining a plurality of patents, which is against the constitutional intent to promote the progress of science and technology and thus against the public policy.

The Examiner asserts that the special technical feature is the pyrrolidinyl moiety. Applicants respectfully disagree. Applicants assert that the "special technical feature" (i.e. the core) should be construed as follows:



M.P.E.P. Section 1850 discusses the Requirement for "Unity of Invention". Subsection D specifically refers to "Markush Practice" wherein it is stated that the requirement of a technical interrelationship and the same or corresponding special technical features as defined in PCT Rule 13.2, shall be considered to be met when the alternatives are of a similar nature. Subsection D further states:

When the Markush grouping is for alternatives of chemical compounds, they shall be regarded as being of a similar nature where the following criteria are fulfilled:

*(A) All alternatives have a common property or activity;*

**and**

*(B)(1) A common structure is present, i.e., a significant structural element is shared by all of the alternatives; or*

*(C)(2) In cases where the common structure cannot be the unifying criteria, all alternatives belong to a recognized class of chemical compounds in the art to which the invention pertains.*

In paragraph (B)(1), above, the words "significant structural element is shared by all of the alternatives" refer to cases where the compounds share a common chemical structure which occupies a large portion of their structures, or in case the compounds have in common only a small portion of their structures, the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. The structural element may be a single component or a combination of individual components linked together (emphasis added).

Applicants assert that the structure shown above is a "significant structural element" shared by all the alternatives. That is, the compounds of claims 30-49 share a common chemical structure which occupies a large portion of their structures. Even if the Examiner should take the position that the compounds have in common only a small portion of their structures, Applicants assert that the commonly shared structure constitutes a structurally distinctive portion in view of existing prior art. Furthermore, the compounds of Claims 39-40 have a common property or activity i.e. the compounds possess dipeptidyl-peptidase-IV enzyme inhibitory activity. Therefore, the Markush grouping for alternatives of chemical compounds should be regarded as being "of a similar nature" under paragraphs (A) and (B)(1) above. Applicants respectfully disagree with the Examiner's contention that the common structure (i.e. in Examiner's words, the

“core structure”) is not the unifying criteria. Applicants assert that the common structure is the unifying criteria.

It would appear that the International Examining Authority also believes that the common structure is the unifying criteria. This invention is a national stage entry of the international application No. PCT/HU03/00017, for which an international preliminary examination report (IPER) has already been established. A copy of the IPER is enclosed herewith for Examiner’s review. The IPER identified only two inventions. The International Preliminary Examining Authority states that the application concerns “N-substituted 1-aminoacetyl-2-cyano-pyrrolidines”. They are as follows:

**Invention I: N-substituted 1-aminoacetyl-2-cyano-pyrrolidines, their use and preparation, and their amino precursors (claims 1-23, 25, 29)**

**Invention II: Pyrrolidine precursors (claims 24, 26-28)**

The International Application was examined for all of the original claims 1-29 presented therein. Instant claims 30-74 in the present application are closely modeled after original claims 1-29 which were the subject of the IPER. Therefore, it is respectfully submitted that: (1) similar standards to those used in the international examination should be used in the examination of the instant application and (2) the restriction requirement should be modified accordingly.

Applicants assert that a search of claims 30-67 in their entirety should not impose any undue burden on the Examiner. Even if the compounds were deemed to fall within several classes or subclasses, this factor alone should not, in and of itself, impose any undue burden on the Examiner in searching the classes together, especially in view of the arguments advanced above concerning the “significant structural element”. Furthermore, the fact that different fields of search may be involved does not establish that a Markush group is improper under *Ex parte Brouard et al.*, 201 U.S.P.Q. 538 (POBA 1976). In particular, the PTO Board of Appeals stated “the fact that [six] different fields of search are involved does not establish that the Markush group is improper.”

Applicants submit that product and the related process claims should be rejoined pursuant to MPEP 821.04. As noted in MPEP 821.04:

"However, if applicant elects claims directed to the product, and a product claim is subsequently found allowable, withdrawn process claims which depend from or otherwise include all the limitations of the allowable product claim will be rejoined." (emphasis added)

Claims 30-49 are compound claims. Claims 50-58 are pharmaceutical composition claims. Claim 59 is a process of making claim. Claims 60-67 are method of using claims. Claim 59 and Claims 60-67 incorporate all the limitations of one or more of the compound claims (i.e. Claims 30-49).

Finally, Applicants respectfully submit that this twenty-two-way restriction imposes an undue expense on the Applicants and discourages Applicants from maintaining a plurality of patents, which is against the constitutional intent to promote the progress of science and technology and thus against the public policy.

In view of the aforesaid comments, Applicants request the reconsideration and withdrawal of the Election/Requirement. Applicants also request that Applicants' specific arguments regarding the impropriety of the Election/Restriction be specifically addressed, if the Election/Restriction is maintained. Furthermore, Applicants request that they be provided with the opportunity to respond to any new bases made in support of the Election/Restriction before the Election/Restriction is made final.

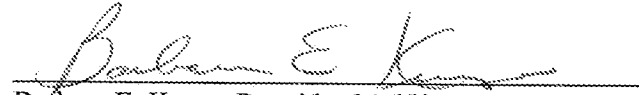
#### Provisional Election

To comply with the Examiner's Election/Restriction requirement, Applicants provisionally elect, with traverse, Group I wherein B is formula (1) or formula (2). Claims 30-34, 38-40, 44-45, 49-54 and 58 read upon Group I. Applicants provisionally elect the species that is Example 4. Example 4 (page 22 of specification) is a compound of general Formula I wherein R1 is 5-cyano-pyridin-2-yl, B is a group of formula (1) i.e. pyridyl and R2 and R3 are both fluorine.

N.B. It appears as though the Examiner incorrectly named the group corresponding to formula (1) and (2). Applicants believe that the Examiner meant to refer to this group as "piperidinyl" not "pyridyl".

Applicants affirm their right to file one or more divisional applications with respect to any of the non-elected subject matter.

Respectfully submitted,

A handwritten signature in cursive script, appearing to read "Barbara E. Kurys", is written over a horizontal line.

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# PATENT COOPERATION TREATY

## PCT



### INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

REC'D 08 JUN 2004

Applicant's or agent's file reference Case 888/PCT	<b>FOR FURTHER ACTION</b> See Notification of Transmittal of International Preliminary Examination Report (Form PCT/PEA/416)	
International application No. PCT/HU 03/00017	International filing date (day/month/year) 04.03.2003	Priority date (day/month/year) 06.03.2002
International Patent Classification (IPC) or both national classification and IPC C07D451.04, C07D451.04		
Applicant SANOFI-SYNTHELABO		

1.	This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
2.	This REPORT consists of a total of 8 sheets, including this cover sheet.  <input checked="" type="checkbox"/> This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).  These annexes consist of a total of 4 sheets.
3.	This report contains indications relating to the following items:  I <input checked="" type="checkbox"/> Basis of the opinion II <input type="checkbox"/> Priority III <input checked="" type="checkbox"/> Non-establishment of opinion with regard to novelty, inventive step and industrial applicability IV <input checked="" type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application

Date of submission of the demand  18.09.2003	Date of completion of this report  07.06.2004
Name and mailing address of the international preliminary examining authority:   European Patent Office - P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk - Pays Bas Tel. +31 70 340 - 2040 Tx: 31 651 epo nl Fax: +31 70 340 - 3016	Authorized Officer  Allard, M  Telephone No. +31 70 340-2002  

# INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/HU 03/00017

## I. Basis of the report

1. With regard to the **elements** of the international application (*Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17)*):

### Description, Pages

1-41 as originally filed

### Claims, Numbers

1-29 as originally filed

### Drawings, Sheets

1/3-3/3 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/HU 03/00017

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

*(Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)*

6. Additional observations, if necessary:

**III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,  
☒ claims Nos. 23, 25 (both partly)

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (specify):  
☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):  
☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.  
☒ no international search report has been established for the said claims Nos. 23, 25 (both partly)

2. A meaningful international preliminary examination cannot be carried out due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

- ☐ the written form has not been furnished or does not comply with the Standard.  
☐ the computer readable form has not been furnished or does not comply with the Standard.

**IV. Lack of unity of invention**

1. In response to the invitation to restrict or pay additional fees, the applicant has:

- ☐ restricted the claims.  
☐ paid additional fees.  
☐ paid additional fees under protest.  
☐ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

- ☐ complied with.



**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT**

International application No. PCT/HU 03/00017

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☒ not complied with for the following reasons:

**see separate sheet**

4. Consequently, the following parts of the international application were the subject of international preliminary examination in establishing this report:

☒ all parts.

☐ the parts relating to claims Nos. .

**V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

1. Statement

Novelty (N)	Yes: Claims	1-22, 24, 26-29
	No: Claims	23, 25
Inventive step (IS)	Yes: Claims	-
	No: Claims	1-29
Industrial applicability (IA)	Yes: Claims	1-29
	No: Claims	-

2. Citations and explanations

**see separate sheet**

**INTERNATIONAL PRELIMINARY  
EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/HU 03/00017

**Reference is made to the following documents:**

- D01: WO 01 96295 A (NOVARTIS AG ET AL) 20 December 2001 (2001-12-20)
- D02: WO 98 19998 A (NOVARTIS AG) 14 May 1998 (1998-05-14)
- D03: AUGUSTYNS KJL ET AL: 'Pyrrolidides: synthesis and structure-activity relationship as inhibitors of dipeptidyl peptidase IV' EUROPEAN JOURNAL OF MEDICINAL CHEMISTRY, vol. 32, no. 4, 1997, pages 301-309, XP004086653
- D04: US-A-4 001 422 (DANILEWICZ JC ET AL) 4 January 1977 (1977-01-04)
- D05: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242778 & J. MED. CHEM., vol. 36, no. 23, 1993, pages 3707-3720,
- D06: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242779 & J. MED. CHEM., vol. 34, no. 2, 1991, pages 656-663,
- D07: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242780 & J. MED. CHEM., vol. 17, 1974, page 739, 742
- D08: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242781 & J. CHEM. SOC. PERKIN TRANS. 1, 1976, page 938
- D09: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242782 & TETRAHEDRON LETT., vol. 40, no. 37, 1999, pages 6745-6748,
- D10: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242783 & YAKUGAKU ZASSHI, vol. 71, 1951, page 1053, 1057
- D11: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242784 & J. HETEROCYCL. CHEM., vol. 19, 1982, pages 485-488,
- D12: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242785 & ARCH. PHARM., vol. 332, no. 11, 1999, pages 389-398,
- D13: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242786 & TETRAHEDRON LETT., vol. 39, no. 20, 1998, pages 3121-3124,

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EXAMINATION REPORT - SEPARATE SHEET**

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International application No. PCT/HU 03/00017

- D14: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242787 & CHEM. BER., vol. 74, 1941, page 1661
- D15: DATABASE CROSSFIRE BEILSTEIN [Online] Beilstein Institut zur Förderung der Chemischen Wissenschaften, Frankfurt am Main, DE; XP002242788 & J. MED. CHEM., vol. 43, no. 11, 2000, pages 2087-2092,
- D16: EP-A-0 156 433 (JANSSEN PHARMACEUTICAL N.V.) 2 October 1985 (1985-10-02)
- D17: WO 99 65895 A (SANOFI-SYNTHELABO) 23 December 1999 (1999-12-23)

**Re Item III**

**Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

With regard to claims 23 and 25 it should be noted that the present international preliminary examination is limited to those parts which have been the subject-matter of a complete international search, i.e. to compounds (II) or (V) wherein R<sup>1</sup> has the meanings recited in claims 8-12.

**Re Item IV**

**Lack of unity of invention**

The present application concerns N-substituted 1-aminoacetyl-2- cyano-pyrrolidines, their use and preparation (claims 1-22, 29).

Furthermore, the application concerns amino intermediates (claims 23 and 25) useful as precursors of the structural amino part of the final products on the one hand, and pyrrolidino intermediates (claims 24 and 26-28) useful as precursors of the structural pyrrolidine part of the final products on the other hand.

In such a combination of intermediates unity is not considered as being present, see "Administrative Instructions under the PCT" S-03/1998, Annex B, Part 1, (g)(vi), in combination with Rules 13.2 and 13.1 PCT.

Following inventions have therefore be identified:

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- **Invention 1:** N-substituted 1-aminoacetyl-2-cyano-pyrrolidines, their use and preparation, and their amino precursors (claims 1-23, 25, 29)
- **Invention 2:** Pyrrolidine precursors (claims 24, 26-28)

**Re Item V**

**Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**

Novelty (Article 33(2) PCT)

**Invention 1**

The subject-matter of claims 23 and 25 lacks novelty in the light of D01 (see page 34, example 2kk), D02 (see page 12, example 17, and page 14, example 66), D04 (see examples 2 and 4), D05-D15, D16 (see example 40), and D17 (see examples 7 and 8).

The subject-matter of claims 1-22 and 29 is not disclosed in the available prior art and is therefore novel.

**Invention 2**

The subject-matter of claims 24 and 26-28 is not disclosed in the available prior art and is therefore novel.

Inventive step (Article 33(3) PCT)

**Invention 1**

The subject-matter of claims 23 and 25 lacking novelty lacks necessarily an inventive step.

The subject-matter of claims 1-22 and partly 29 lacks also an inventive step for the following reasons:

D01, which is considered to represent the closest prior art, describes substituted 1-glycyl-2-cyanopyrrolidines useful as DPP-IV inhibitors. D02 discloses similar

**INTERNATIONAL PRELIMINARY  
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International application No. PCT/HU 03/00017

compounds with the same activity.

In the light of the teachings of D01, the problem underlying and possibly solved by the present application (see description page 13, lines 11 and 12) can be seen in the provision of further DPP-IV inhibiting cyanopyrrolidines having the same level of biological activity.

To solve this problem, the present application proposes to replace in the compounds disclosed in D1 the 2-cyanopyrrolidine moiety by a 4-fluoro- or 4,4-difluoro-2-cyanopyrrolidine moiety.

It is however already known from D03 that 4-fluoro-pyrrolidines can constitute a building block for DPP-IV inhibitors of structure comparable to the structure of the compounds of the present application.

The solution proposed by the present application appears therefore to be an obvious measure in the design of further DPP-IV inhibitors with the same level of activity, which does not involve an inventive step.

It is noted that the very general statement at page 13, lines 11 and 12, of the present application is not convincing to demonstrate that the problem of providing derivatives with improved activity has indeed be solved by the application.

## **Invention 2**

The structure of the intermediates of claims 24, 26-28 and partly 29 is imposed by the structure of the aimed end-products: in the absence of an inventive step for these end-products, such intermediates, and consequently the subject-matter of claims 24, 26-28 and partly 29, lack also an inventive step.

### Industrial applicability (Article 33(4) PCT)

## **Invention 1 and invention 2**

The compounds, compositions and processes of claims 1-29 can be used in the pharmaceutical industry.